CHAPTER II
RATIONALE

Isolated arrested heart model

The isolated heart model developed by Langendoff is a model which eliminates systemic reflex effects. This model is free of central neural and hormonal effects and has been employed in numerous studies of cardiac function, metabolism, ultrastructure and hemodynamics. Moreover, pharmacologic studies have also been performed using isolated heart preparation. In this preparation, coronary perfusion is started in situ to avoid ischemic damage to the heart. The studies of coronary circulation by using perfusate containing elevated potassium (40 mM) have found that the heart was arrested. Cardiac arrest greatly reduces myocardial metabolism and allows direct visualization of coronary microcirculation. This model is appropriate for both physiologic and pharmacologic studies. It is particularly well suited for determining the direct effects of an intervention on coronary tone and the coronary microcirculation. Since the heart is arrested, changes in heart rate and contractility do not complicate measurements of coronary tone (McDonagh, 1983; McDonagh et al.,1984).

Streptozotocin (STZ)- treated rat model

The STZ-treated rat was selected as a diabetic model used in this study because of this model closely resembles to insulin-dependent diabetes mellitus in humans. The molecular structure of STZ was shown in Figure2. STZ-induced beta-cells damage by initiating biochemical events which cause DNA strand breaks. STZ exerts its initial biochemical effects by the generation of highly reactive carbonium ions (CH_3^+). These ions are able to produce nonspecific damage in beta-cells by catching with alkylating DNA bases at various positions. As part of this process to repair these lesions the poly (ADP-ribose) system is activated and NAD is critically depleted (Wilson et al., 1984; Rofkin and Porte, 1991). Moreover, STZ also is

able to cause beta-cells specific damage via its ability to interact with the glucose-sensing mechanism of the beta-cells. STZ accomplishes this by its glucose moiety. This interaction with the glucose recognition system would allow the toxin to be sequestered differently in beta-cells than in other cells and, therefore, cause beta-cells specific damage. Beta-cells damage by using STZ is the combination of the beta-cells specific and nonspecific damage that leads to the ultimate death of the cells (Ledoux et al., 1988; Rofkin and Porte, 1991).

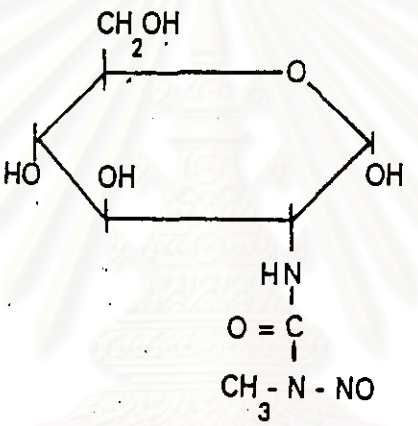

Fig. 2 Molecular structure of streptozotocin or 2 - deoxy - 2 (3 - methyl - nitrosoureido) - D - glucopyranose . (Rofkin and Porte , 1991)